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Progeria: Translational insights from cell biology

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Cell biologists love to think outside the box, pursuing many surprising twists and unexpected turns in their quest to unravel the mysteries of how cells work. But can cell biologists think outside the bench? We are certain that they can, and clearly some already do. To encourage more cell biologists to venture into the realm of translational research on a regular basis, we would like to share a handful of the many lessons that we have learned in our effort to develop experimental treatments for Hutchinson-Gilford progeria syndrome (HGPS), an endeavor that many view as a "poster child" for how basic cell biology can be translated to the clinic.

The first lesson gained from our studies of Hutchinson-Gilford progeria syndrome (HGPS) sounds simple enough: Approach any translational opportunity that may cross your path with an inquisitive mind. However, because it is nearly impossible to predict when, where, or how such opportunities might arise, the challenge is to remain open to the potential at all times and in all places.

For example, the seeds of our collaboration were sown about a decade ago at a decidedly nonscientific venue: a cocktail party in Washington, D.C. During the event, the genomic researcher among us (Collins) happened to strike up a conversation with a young emergency room physician (Scott Berns) doing a White House Fellowship. The ER doctor mentioned that he and his physician-scientist wife (Gordon) had a young son with HGPS, which is a rare, genetic disease characterized by rapid, premature aging (Gordon et al., 2003). The molecular cause of HGPS was unknown at the time, making the search for potential treatments and cures all but impossible. Berns told Collins that the couple had founded The Progeria Research Foundation to encourage scientists to work on this formidable challenge. After a few more conversations, the genomic researcher was "hooked," and agreed to help organize a workshop

to help track down the genetic mutation responsible for HGPS. Pretty soon his laboratory joined in.

So, what does it take to hook basic researchers on translational challenges? There are a few elements that strike us as crucial, perhaps even essential, to motivating basic scientists to apply their work toward clinical problems. Among the foremost is human need. In the case of HGPS, the need was obvious: there was no treatment for the disease, and patients died from cardiovascular disease at around age 13. Another key motivator is intellectual challenge. Nature may pose much tougher research questions than we can dream up ourselves, as we have learned time and time again in our decade of studying HGPS.

We must also recognize the motivating force of technological innovation. Clinical problems once considered too difficult or time-consuming to be tackled by basic research can become amenable to solution thanks to the development of new tools and technologies. In the genomic sector, such innovation includes databases containing the reference sequence of the human genome, maps of human genetic variation, and ever-expanding catalogs of human genotype/phenotype correlations. Fueling this tsunami of genomic discovery are technologies that have dramatically cut the cost of DNA sequencing from \$100 million per genome in 2001 to less than \$8,000 today.

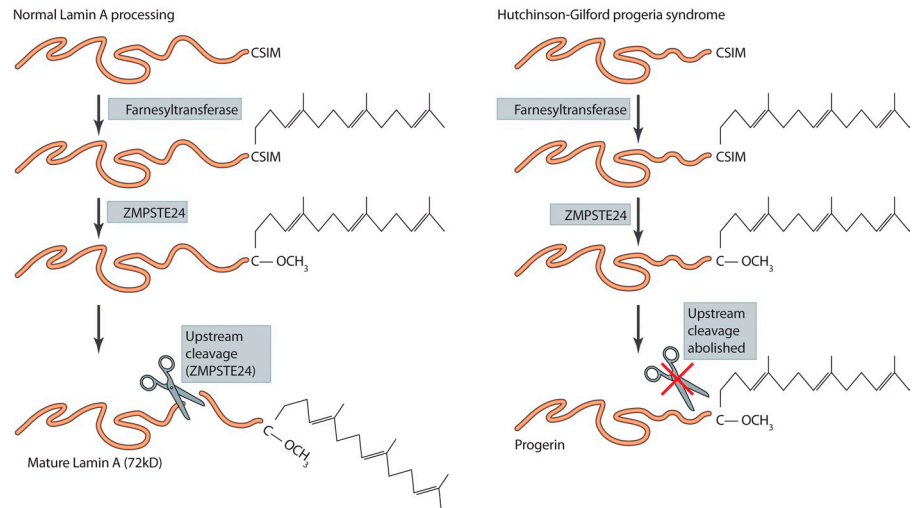
Cell biology, too, has benefitted greatly from technological advances over the past decade. These advances include the development of the spinning disk and other advanced confocal microscopes that, along with higher speed cameras, make it possible to record 3D images in living cells over long periods of time (Gerlich and Ellenberg, 2003). Using the techniques of photobleaching and photoactivation, new fluorophores with a variety of excitation wavelengths have also provided additional tools to label and track how proteins behave in living cells (Lippincott-Schwartz et al., 2003; Miyawaki et al., 2003). In addition to better imaging tools, cell biologists now have access to many more wet-bench biochemical assays and kits for determining various cellular processes, including apoptosis, senescence, protein phosphorylation, ATP production, and cell stress. These types of tools have been essential for dissecting out the molecular mechanisms underlying HGPS.

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Abbreviations used in this paper: FTL, farnesyltransferase inhibitor; HGPS, Hutchinson-Gilford progeria syndrome.

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Figure 1. Posttranslational processing of lamin A. A farnesyl group is added to the C terminus of the lamin A protein by the enzyme farnesyltransferase, and, subsequently, the last three amino acids are cleaved by the endoprotease ZMPSTE24. ZMPSTE24 then removes the terminal 15 amino acids, a step that is blocked in HGPS because of the internal deletion of the cleavage site in the progerin protein.



Get to the root of the problem

Our second lesson is often easier said than done: get to the root of the problem. When confronted with heartbreaking human need and urgent clinical challenges, it is tempting to race ahead to exploring therapeutic possibilities before gaining a firm, or even tentative, grasp on the molecular roots of a disease. But much time, money, and, ultimately, lives may be lost if a translational research team rushes into clinical trials without a basic understanding of the molecular mechanisms underlying the disease in question.

In the case of HGPS, we were fortunate that it only took us a couple of years to get the proverbial cart hooked up to the horse and heading in the right direction. In 2003, through a combination of hard work and serendipity, the Collins laboratory discovered that HGPS is caused by a C-to-T point mutation near the end of the lamin A (*LMNA*) gene (Eriksson et al., 2003). The point mutation activated a splice donor in the middle of an exon, leading to the production of an abnormal protein, now called progerin, that is 50 amino acids shorter than normal (Fig. 1).

Since the gene discovery, understanding of HGPS has advanced at a rapid pace, fueled by basic research using both in vitro and animal models of disease. This understanding has opened many doors; some were expected, others unexpected, with some leading to exciting translational strategies and others pointing us back to the basics of human biology. How we set about exploring what lay beyond these doors leads us to our third lesson.

Build upon previous knowledge

U.S. President Woodrow Wilson once remarked, “I not only use all the brains I have, but all that I can borrow.” In the case of HGPS, although the earliest iteration of our team was made up primarily of genomic researchers, molecular biologists, and clinical researchers, we soon realized the need to access the impressive body of knowledge offered to us by cell biology.

Once we discovered that the *LMNA* gene was the culprit in HGPS, nearly two decades of lamin A cell biology provided almost immediate insights about how this mutation might cause disease in a dominant fashion. Lamin A is posttranslationally

modified (Fig. 1), with the addition of a farnesyl group at the C terminus that seems to assist in “zip-coding” the protein to the inner surface of the nuclear membrane. The protein then needs to be released from this tether, which is accomplished by an enzyme called ZMPSTE24. The abnormal splice event that gives rise to progerin eliminates the ZMPSTE24 cleavage, so progerin remains permanently farnesylated. To explore the cell biological consequences, we forged a rewarding collaboration with Robert Goldman, noted for his lamin A work. His laboratory helped us to document quickly the consequences of *LMNA* mutations at the cellular level, including abnormal nuclear morphology, premature senescence, and loss of peripheral heterochromatin (Fig. 2, A, D, and E; Goldman et al., 2004). It also became clear that we needed more cell biology expertise within our own group, and, in 2005, the Collins laboratory recruited a postdoc (Cao) with a strong background in cell biology research. The move paid off, and subsequent work showed effects of *LMNA* mutations on mitosis, causing incomplete disassembly of nuclear envelope, chromosome missegregation, and binucleation (Fig. 2, B and C; Cao et al., 2007; Dechat et al., 2007).

Our pathway from bench to clinic has been illuminated by the brilliance of a diverse array of scientists, including seminal papers describing the genomic instability in HGPS (Liu et al., 2005) and the mechanical changes in the lamina of HGPS cells (Dahl et al., 2006). Likewise, several groups have generated induced pluripotent stem (iPS) cells from HGPS patients, providing all of us in the field with a powerful new tool for studying the pathogenesis of HGPS and testing new therapeutic strategies (Liu et al., 2011; Zhang et al., 2011; Progeria Research Foundation, 2012).

Clinical consequences: Time is of the essence

Like most biomedical researchers, cell biologists aspire to see their discoveries turned into better health outcomes as swiftly as possible. However, in our experience, the translational clock usually ticks faster when there is a clinician on the translational team who is acutely aware of how short the timeline is for many who suffer from lethal, progressive diseases, or when basic

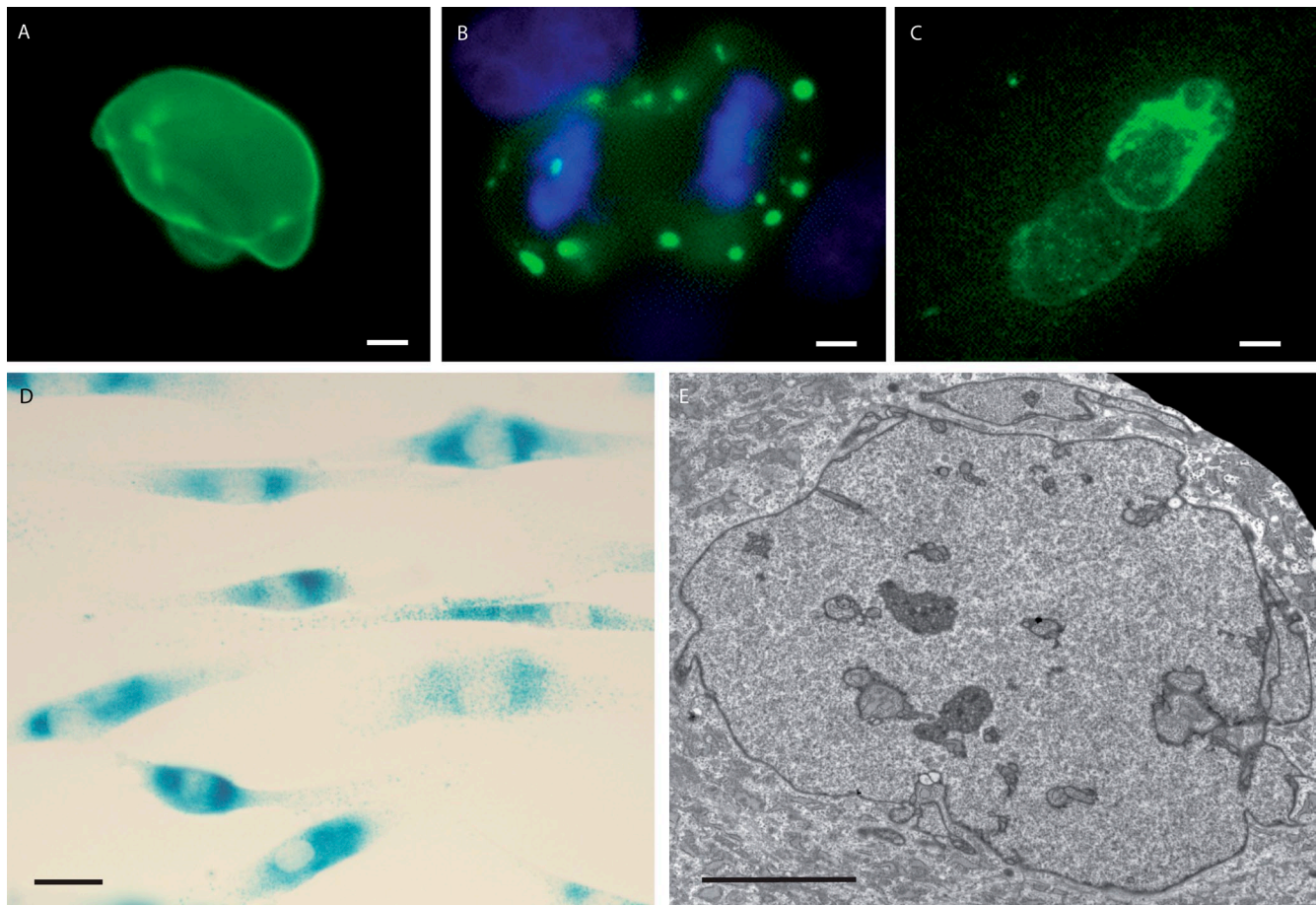


Figure 2. Defects in HGPS cells. (A) Abnormal nuclear morphology (nuclear blebbing). A nucleus of a passage 17 HGPS cell (HGADFN167) was stained in green with an anti-lamin A/C antibody. (B) Mitotic defects. Nuclear disassembly is incomplete at the onset of mitosis. Progerin (green signal) forms giant aggregates in mitotic cytoplasm. DNA is stained in blue. (C) Binucleation. A binucleated HGPS cell (HGADFN167) stained with an anti-progerin antibody is shown in green. (D) Premature senescence. Senescence-associated β -galactosidase staining is shown for HGPS cells (HGADFN167) at passage 17. (E) Loss of peripheral heterochromatin and extensive nuclear disorganization of a passage 18 HGPS cell (HGADFN167). Source of cells: the Progeria Research Foundation Cell and Tissue Bank (Providence, RI). A, D, and E are courtesy of K. Cao. B and C are from Cao et al. (2007), copyright the National Academy of Sciences. Bars: (A–C and E) 5 μ m; (D) 20 μ m.

scientists interact with patients and their families through meetings organized by advocacy groups (Gordon et al., 2008).

While our discovery of the *LMNA* mutation and elucidation of its mechanism of action raised a host of fascinating questions that could fuel years of basic research, we also knew that time was of the essence for children with HGPS and their families. Because HGPS is so rare, and many HGPS patients are in fragile health, there are very limited opportunities to conduct human trials of potential therapies. Consequently, we needed to select and use the scientific tools at our disposal in highly strategic ways if we were to move forward expeditiously.

Theory predicted that farnesyltransferase inhibitors (FTIs) would be of potential use in HGPS by reducing the amount of permanently farnesylated progerin, so that is where we began. Tests in cell culture by the Collins laboratory and others showed that FTIs can significantly ameliorate the nuclear-shape abnormalities seen in HGPS cells (Capell et al., 2005). However, cells could only take us so far in the preclinical space. We also needed a good animal model with the precise genetic mutation seen in humans or, even better, a number of genetically precise models created via multiple strategies.

Our group developed a mouse model of HGPS by re-engineering human *LMNA* to carry the HGPS mutation, and then inserting it into the mouse germline (Varga et al., 2006). Our mice lack the skin, hair, or bone abnormalities seen in humans with HGPS, but, like the human patients, exhibit progressive loss of vascular smooth muscle cells in the media of large arteries. Tests of FTIs in this and other mouse models (Fong et al., 2006; Capell et al., 2008) complemented other data in support of an initial clinical trial that administered an FTI, lonafarnib, to HGPS patients (Fig. 3). Other work provided an evidence-based rationale (Varela et al., 2008) for a second generation of clinical trials that combined FTIs with statins and bisphosphonates.

Nonclinicians embarking on translational research projects would also do well to acquaint themselves with another powerful time saver: studies of the natural history of the disease in humans. Well-conducted natural history studies can define the range of manifestations and progression of rare conditions, and also identify biomarkers and other correlates of clinical outcomes that can be used to design an effective clinical trial. In the case of HGPS, such studies were limited, and so efforts to identify statistically reliable outcome measures (Gordon et al., 2007,



Figure 3. **Children with HGPS.** Participants in a clinical trial of an FTL. Photographs courtesy of The Progeria Research Foundation.

2011; Merideth et al., 2008; Gerhard-Herman et al., 2012) had to proceed simultaneously with the planning and implementation of treatment trials.

Our therapeutic efforts may soon extend to a third generation of HGPS clinical trials. Work in cell culture supports the possibility that an analogue of rapamycin, an FDA-approved immunosuppressant drug used to prevent rejection in organ transplantation, may provide benefit if added to the current combination approach. The nuclear morphology analysis work that provided a quantitative assessment of treatment effectiveness also highlights how cell biology can serve to guide, not just support, translational strategies (Cao et al., 2011a; Driscoll et al., 2012).

Readers will have noted that all of these therapeutic ideas have been based upon repurposing drugs originally developed for other purposes. But that is not the only option. Led by a better understanding of the basic biology of HGPS, concurrent investigations on high throughput assay and drug development (Auld et al., 2009), gene therapy (Scaffidi and Misteli, 2005; Osorio et al., 2011), and stem cell treatment (Wenzel et al., 2012) may all provide future opportunities for combating, and perhaps even curing, HGPS.

Translational research may yield basic insights

Although the primary goal of translational research is helping patients, basic researchers going after this goal may also find themselves rewarded with unexpected insights into fundamental biological processes. In our case, the translation-oriented discovery of the HGPS mutation paved the way for a series of cell biology studies that demonstrated that progerin is also made in normal cells. The splice site activated in HGPS to create progerin is actually used at a low level in normal cells, and becomes more active as cell senescence approaches (Scaffidi and Misteli, 2006; McClintock et al., 2007; Olive et al., 2010). This splice site even may play a role in normal development, such as in closure of the ductus arteriosus (Bökenkamp et al., 2011). Most recently, our work suggests that use of this splice site is somehow triggered by shortened telomeres, hastening the irreversible process of cellular senescence (Cao et al., 2011b).

These findings establish HGPS as a valid model system for future basic research into aging.

The example of HGPS should make it clear that translational science is not just a one-way street, with basic research discoveries flowing from the bench toward more applied research in the clinic. Rather, the translational process is a virtuous circle, in which basic science benefits clinical research and vice versa. In the span of a decade, HGPS has gone from being a rare and mostly ignored disorder to being “hot science” in both basic and clinical journals. If clinical researchers had not persuaded basic researchers to devote significant effort to solving the translational riddle posed by HGPS, the entire biology community might have missed out on a valuable window into development, senescence, and aging.

You can do it too!

Although this is still a work in progress, we think HGPS is a translational success story worth repeating, and we would like to encourage more cell biologists to give it a try. With more than 4,500 human conditions now having their molecular causes defined, many scientists working on basic research into particular genes, proteins, or pathways may have new opportunities to make these translational connections. For cell biologists who are considering heading down the translational pathway, we suggest checking out the Online Mendelian Inheritance in Man database (<http://www.omim.org/>) to see what disorders might now connect to their work. We also encourage cell biologists to reach out to clinicians and patient advocacy organizations to seek potential collaborations, as well as to welcome the occasions when they reach out.

It is true that serendipity played a significant role for HGPS, and that does not always happen. But we do view our experience as a beacon of hope that shows what basic and clinical researchers can accomplish when they join together to tackle a translational challenge. The scientific opportunities have never been better. We look forward to seeing what cell biology can do in the next few years to help us light up more of these beacons for the millions of people awaiting treatments and cures.

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